CLAIMS

We claim:

1. A method for increasing contractile function in the heart of a patient, comprising delivering a transgene encoding an angiogenic protein or peptide to the myocardium of the patient by introducing a vector comprising the transgene into at least one coronary artery, wherein the transgene is delivered to the myocardium and expressed, and contractile function in the heart is increased.

2. The method of claim 1, wherein the vector is introduced from a catheter conducted into the lumen of one or more coronary arteries.

3. The method of claim 2, wherein the vector is injected from the tip of said catheter.

4. The method of claim 1, wherein the introduction of vector comprises injecting the vector into the lumen of at least two coronary arteries supplying blood to the myocardium.

5. The method of claim 4, wherein the vector is introduced into at least one right coronary artery and at least one left coronary artery.

6. The method of claim 3, wherein the vector is introduced by injection from a catheter conducted at least about 1 cm into the lumen of said arteries.

7. The method of claim 6, wherein the vector is introduced into at least one right coronary artery and at least one left coronary artery.

8. The method of claim 1, wherein the vector is also introduced into a saphenous vein graft and/or an internal mammary artery graft supplying blood to the myocardium.

9. The method of claim 1, wherein the vector is introduced by retrograde perfusion from a catheter placed into a conduit receiving blood from the myocardium.

10. The method of claim 1, wherein said vector is a viral vector.

11. The method of claim 10, wherein said vector is a replication-deficient viral vector.

12. The method of claim 10, wherein said vector is an adenovirus vector.

13. The method of claim 12, wherein said vector is a replication-deficient adenovirus vector.

14. The method of claim 12, wherein about 10^7 to about 10^{13} adenovirus vector particles are delivered in vivo.

15. The method of claim 14, wherein about 10^9 to about 10^{12} adenovirus vector particles are delivered in vivo.

16. The method of claim 1, wherein expression of said transgene is driven by a CMV promoter which is contained in the vector.

17. The method of claim 1, wherein expression of said transgene is driven by a tissue-specific promoter which is contained in the vector.

18. The method of claim 17, wherein expression of said transgene is driven by a cardiomyocyte-specific promoter which is contained in the vector.

19. The method of claim 18, wherein said cardiomyocyte-specific promoter is selected from the group consisting of a cardiomyocyte-specific myosin light chain promoter and a cardiomyocyte-specific myosin heavy chain promoter.

20. The method of claim 1, wherein said angiogenic protein or peptide is selected from the group consisting of a fibroblast growth factor, a vascular endothelial growth factor, a platelet-derived growth factor and an insulin-like growth factor.

21. The method of claim 1, wherein said angiogenic protein or peptide is a fibroblast growth factor.

22. The method of claim 21, wherein said angiogenic protein or peptide is a fibroblast growth factor selected from the group consisting of aFGF, bFGF, FGF-4, FGF-5 and FGF-6.

23. The method of claim 1, wherein said angiogenic protein is a vascular endothelial growth factor.

24. The method of claim 23, wherein said vascular endothelial growth factor is selected from the group consisting of a VEGF-A, a VEGF-B and a VEGF-C.

25. The method of claim 1, wherein said angiogenic protein or peptide is an insulin-like growth factor.

26. The method of claim 25, wherein said angiogenic protein or peptide is insulin-like growth factor 1.

27. The method of claim 1, wherein said angiogenic protein or peptide comprises a signal peptide.

28. The method of claim 1, wherein said angiogenic protein or peptide is an angiogenic polypeptide regulator.

29. The method of claim 1, wherein said vector further comprises a second transgene encoding an angiogenic protein or peptide.

30. The method of claim 1, wherein said vector comprises a transgene or transgenes encoding at least two angiogenic proteins or peptides.

31. The method of claim 30, wherein said angiogenic proteins or peptides are each independently selected from the group consisting of a fibroblast growth factor, a vascular endothelial growth factor, a platelet-derived growth factor and an insulin-like growth factor.

32. The method of claim 30, wherein said angiogenic proteins or peptides are each independently selected from the group consisting of a fibroblast growth factor, a vascular endothelial growth factor, a platelet-derived growth factor, an insulin-like growth factor, a hypoxia-inducible factor and an angiogenic polypeptide regulator.

33. The method of claim 30, wherein the first of said angiogenic proteins or peptides is selected from the group consisting of a fibroblast growth factor, a vascular endothelial growth factor, a platelet-derived growth factor, a hypoxia-inducible factor, an insulin-like growth factor and an angiogenic polypeptide regulator and wherein the second of said angiogenic proteins or peptides is selected from another member of said group.

34. The method of claim 30, wherein the first of said angiogenic proteins or peptides is a fibroblast growth factor and the second of said angiogenic proteins or peptides is

a vascular endothelial growth factor.

35. The method of claim 30, wherein the first of said angiogenic proteins or peptides is a fibroblast growth factor or a vascular endothelial growth factor and the second of said angiogenic proteins or peptides is an insulin-like growth factor.

36. The method of claim 30, wherein said vector comprises a transgene or transgenes encoding a fibroblast growth factor, a vascular endothelial growth factor and an insulin-like growth factor.

37. The method of claim 1, wherein said vector further comprises a transgene encoding a cardiac enhancing protein or peptide.

38. The method of claim 37, wherein said cardiac enhancing protein or peptide is a beta-adrenergic signaling protein or peptide (beta-ASP).

39. The method of claim 37, wherein said cardiac enhancing protein or peptide induces the growth or function of myocytes, thereby enhancing contractile function in the heart.

40. The method of claim 1, wherein said angiogenic protein or peptide stimulates collateral vessel development in the heart, thereby enhancing blood flow in the heart.

41. The method of claim 1, wherein delivery of the transgene using said vector is predominantly localized to the heart.

42. The method of claim 1, wherein said vector predominantly transfects cardiac cells.

43. The method of claim 1, wherein expression of said transgene occurs predominantly within the myocardium.

44. The method of claim 43, wherein expression of said transgene occurs predominantly within cardiac myocytes.

45. The method of claim 1, wherein percent wall thickening in the heart is increased.

46. A method according to one of claims 1 to 45, wherein the step of introducing a vector into at least one coronary artery is performed coincident with or following infusion of the artery with a vasoactive agent.

47. The method of claim 46, wherein said vasoactive agent is infused into the artery at least about 2 minutes prior to the injection of said vector

48. The method of claim 46, wherein the vasoactive agent is histamine or a histamine agonist or a vascular endothelial growth factor (VEGF) protein.

49. The method of claim 48, wherein the vasoactive agent is histamine or a histamine agonist.

50. The method of claim 49, wherein the vasoactive agent is histamine at a concentration of about 1 to 75 micrograms/ml.

51. The method of claim 50, wherein the vasoactive agent is histamine at a concentration of about 25 micrograms/ml infused into the artery at a rate of approximately 1 ml/min for about 3 minutes prior to the injection of said vector.

52. The method of claim 1, wherein said patient has cardiovascular disease.

53. The method of claim 52, wherein said patient has atherosclerosis.

54. The method of claim 52, wherein said patient has myocardial ischemia.

55. A method according to one of claims 1 to 45 or 52 to 54, wherein said patient is a human.

56. The method of claim 55, wherein blood flow within the heart is increased.

57. A method for increasing blood flow in an ischemic tissue of a patient, comprising delivering a transgene encoding an angiogenic protein or peptide to an ischemic region of said tissue by introducing a vector comprising the transgene to said tissue, whereby the transgene is expressed in the tissue, and blood flow in the tissue is increased.

58. The method of claim 57, wherein the vector is introduced into a tissue by anterograde perfusion from a catheter placed into a conduit delivering blood to the tissue.

59. The method of claim 57, wherein the vector is introduced into a tissue by retrograde perfusion from a catheter placed into a conduit receiving blood from the tissue.

60. The method of claim 57, wherein the ischemic tissue comprises muscle cells and wherein increasing blood flow within the ischemic tissue results in increased contractile function.

61. The method of claim 60, wherein the muscle cells are cardiac myocytes.

62. The method of claim 62, wherein the blood vessel is selected from the group consisting of a coronary artery and a femoral artery.

63. The method of claim 57, wherein the vector is introduced by injecting a solution comprising the vector into skeletal muscle, wherein the angiogenic protein or peptide causes an increase in blood flow and a decrease in ischemia in the tissue.

64. The method of claim 63, wherein said solution comprises at least about one ml.

65. The method of claim 57, wherein the patient has cardiovascular disease.

66. The method of claim 65, wherein the patient has peripheral vascular disease.

67. The method of claim 57, wherein the vector is introduced from a catheter conducted into the lumen of one or more coronary arteries.

68. The method of claim 57, wherein the introduction of vector comprises injecting the vector into the lumen of at least two coronary arteries supplying blood to the myocardium.

69. The method of claim 68, wherein the vector is introduced into at least one right coronary artery and at least one left coronary artery.

70. The method of claim 68, wherein the vector is introduced by injection from a catheter conducted at least about 1 cm into the lumen of said arteries.

71. The method of claim 70, wherein the vector is introduced into at least one right coronary artery and at least one left coronary artery.

72. The method of claim 66, wherein the vector is also introduced into a saphenous vein graft and/or an internal mammary artery graft supplying blood to the myocardium.

73. The method of claim 57, wherein the vector is introduced by retrograde perfusion from a catheter placed into a conduit receiving blood from the myocardium.

74. The method of claim 57, wherein said vector is a viral vector.

75. The method of claim 74, wherein said vector is a replication-deficient viral vector.

76. The method of claim 74, wherein said vector is an adenovirus vector.

77. The method of claim 76, wherein said vector is a replication-deficient adenovirus vector.

78. The method of claim 76, wherein about 10^7 to about 10^{13} adenovirus vector particles are delivered in vivo.

79. The method of claim 78, wherein about 10^9 to about 10^{12} adenovirus vector particles are delivered in vivo.

80. The method of claim 57, wherein expression of said transgene is driven by a CMV promoter which is contained in the vector.

81. The method of claim 57, wherein expression of said transgene is driven by a tissue-specific promoter which is contained in the vector.

82. The method of claim 81, wherein expression of said transgene is driven by a cardiomyocyte-specific promoter which is contained in the vector.

83. The method of claim 82, wherein said cardiomyocyte-specific promoter is selected from the group consisting of a cardiomyocyte-specific myosin light chain promoter and a cardiomyocyte-specific myosin heavy chain promoter.

84. The method of claim 57, wherein said angiogenic protein or peptide is selected from the group consisting of a fibroblast growth factor, a vascular endothelial growth factor, a platelet-derived growth factor and an insulin-like growth factor.

85. The method of claim 57, wherein said angiogenic protein or peptide is a fibroblast growth factor.

86. The method of claim 85, wherein said angiogenic protein or peptide is a fibroblast growth factor selected from the group consisting of aFGF, bFGF, FGF-4, FGF-5 and FGF-6.

87. The method of claim 57, wherein said angiogenic protein is a vascular endothelial growth factor.

88. The method of claim 87, wherein said vascular endothelial growth factor is selected from the group consisting of a VEGF-A, a VEGF-B and a VEGF-C.

89. The method of claim 57, wherein said angiogenic protein or peptide is an insulin-like growth factor.

90. The method of claim 89, wherein said angiogenic protein or peptide is insulin-like growth factor 1.

91. The method of claim 57, wherein said angiogenic protein or peptide comprises a signal peptide.

92. The method of claim 57, wherein said angiogenic protein or peptide is an angiogenic polypeptide regulator.

93. The method of claim 57, wherein said vector further comprises a second transgene encoding an angiogenic protein or peptide.

94. The method of claim 57, wherein said vector comprises a transgene or transgenes encoding at least two angiogenic proteins or peptides.

95. The method of claim 94, wherein said angiogenic proteins or peptides are each independently selected from the group consisting of a fibroblast growth factor, a vascular endothelial growth factor, a platelet-derived growth factor and an insulin-like growth factor.

96. The method of claim 94, wherein said angiogenic proteins or peptides are each independently selected from the group consisting of a fibroblast growth factor, a vascular endothelial growth factor, a platelet-derived growth factor, an insulin-like growth factor, a hypoxia-inducible factor and an angiogenic polypeptide regulator.

97. The method of claim 94, wherein the first of said angiogenic proteins or peptides is selected from the group consisting of a fibroblast growth factor, a vascular endothelial growth factor, a platelet-derived growth factor, a hypoxia-inducible factor, an insulin-like growth factor and an angiogenic polypeptide regulator and wherein the second of

said angiogenic proteins or peptides is selected from another member of said group.

98. The method of claim 94, wherein the first of said angiogenic proteins or peptides is a fibroblast growth factor and the second of said angiogenic proteins or peptides is a vascular endothelial growth factor.

99. The method of claim 94, wherein the first of said angiogenic proteins or peptides is a fibroblast growth factor or a vascular endothelial growth factor and the second of said angiogenic proteins or peptides is an insulin-like growth factor.

100. The method of claim 94, wherein said vector comprises a transgene or transgenes encoding a fibroblast growth factor, a vascular endothelial growth factor and an insulin-like growth factor.

101. The method of claim 57, wherein said vector further comprises a transgene encoding a cardiac enhancing protein or peptide.

102. The method of claim 101, wherein said cardiac enhancing protein or peptide is a beta-adrenergic signaling protein or peptide (beta-ASP).

103. The method of claim 101, wherein said cardiac enhancing protein or peptide induces the growth or function of myocytes, thereby enhancing contractile function in the heart.

104. The method of claim 57, wherein said angiogenic protein or peptide stimulates collateral vessel development in the heart, thereby enhancing blood flow in the heart.

105. The method of claim 57, wherein delivery of the transgene using said vector is predominantly localized to the heart.

106. The method of claim 57, wherein said vector predominantly transfects cardiac cells.

107. The method of claim 57, wherein expression of said transgene occurs predominantly within the myocardium.

108. The method of claim 107, wherein expression of said transgene occurs predominantly within cardiac myocytes.

109. The method of claim 57, wherein percent wall thickening in the heart is increased.

110. A method according to one of claims 52 to 54 or 57 to 109, wherein the step of introducing a vector into at least one coronary artery is performed coincident with or following infusion of the artery with a vasoactive agent.

111. The method of claim 110, wherein said vasoactive agent is infused into the artery at least about 2 minutes prior to the injection of said vector.

112. The method of claim 110, wherein the vasoactive agent is histamine or a histamine agonist or a vascular endothelial growth factor (VEGF) protein.

113. The method of claim 112, wherein the vasoactive agent is histamine or a histamine agonist.

114. The method of claim 113, wherein the vasoactive agent is histamine at a concentration of about 1 to 75 micrograms/ml.

115. The method of claim 114, wherein the vasoactive agent is histamine at a concentration of about 25 micrograms/ml infused into the artery at a rate of approximately 1 ml/min for about 3 minutes prior to the injection of said vector.

116. The method of claim 57, wherein the patient has cardiovascular disease.

117. The method of claim 116, wherein said patient has atherosclerosis.

118. The method of claim 116, wherein said patient has myocardial ischemia.

119. A method according to one of claims 57 to 109 or 116 to 118, wherein said patient is a human.

120. The method of claim 119, wherein contractile function within the tissue is increased.

121. A gene therapy composition comprising a vector containing a transgene encoding an angiogenic protein or peptide.

122. The composition of claim 121, wherein said vector is a viral vector.

123. The composition of claim 122, wherein said vector is a replication-deficient viral vector.

124. The composition of claim 122, wherein said vector is an adenovirus vector.

125. The composition of claim 124, wherein said vector is a replication-deficient adenovirus vector.

126. The composition of claim 124, comprising about 10^7 to about 10^{13} adenovirus vector particles.

127. The composition of claim 126, comprising about 10^9 to about 10^{12} adenovirus vector particles.

128. The composition of claim 121, wherein expression of said transgene is driven by a CMV promoter which is contained in the vector.

129. The composition of claim 121, wherein expression of said transgene is driven by a tissue-specific promoter which is contained in the vector.

130. The composition of claim 129, wherein expression of said transgene is driven by a cardiomyocyte-specific promoter which is contained in the vector.

131. The composition of claim 130, wherein said cardiomyocyte-specific promoter is selected from the group consisting of a cardiomyocyte-specific myosin light chain promoter and myosin heavy chain promoter.

132. The composition of claim 121, wherein said angiogenic protein or peptide is selected from the group consisting of a fibroblast growth factor, a vascular endothelial growth factor, a platelet-derived growth factor and an insulin-like growth factor.

133. The composition of claim 121, wherein said angiogenic protein or peptide is a fibroblast growth factor.

134. The composition of claim 133, wherein said angiogenic protein or peptide is a fibroblast growth factor selected from the group consisting of aFGF, bFGF, FGF-4, FGF-5 and FGF-6.

135. The composition of claim 121, wherein said angiogenic protein is a vascular endothelial growth factor.

136. The composition of claim 135, wherein said vascular endothelial growth factor is selected from the group consisting of a VEGF-A, a VEGF-B and a VEGF-C.

137. The composition of claim 121, wherein said angiogenic protein or peptide is an insulin-like growth factor.

138. The composition of claim 137, wherein said angiogenic protein or peptide is insulin-like growth factor 1.

139. The composition of claim 121, wherein said angiogenic protein or peptide comprises a signal peptide.

140. The composition of claim 121, wherein said angiogenic protein or peptide is angiogenic polypeptide regulator.

141. The composition of claim 121, wherein said vector further comprises a second transgene encoding an angiogenic protein or peptide.

142. The composition of claim 121, wherein said vector comprises a transgene or transgenes encoding at least two angiogenic proteins or peptides.

143. The composition of claim 142, wherein said angiogenic proteins or peptides are each independently selected from the group consisting of a fibroblast growth factor, a vascular endothelial growth factor, a platelet-derived growth factor and an insulin-like growth factor.

144. The composition of claim 142, wherein said angiogenic proteins or peptides are each independently selected from the group consisting of a fibroblast growth factor, a vascular endothelial growth factor, a platelet-derived growth factor, an insulin-like growth factor, a hypoxia-inducible factor and an angiogenic polypeptide regulator.

145. The composition of claim 142, wherein the first of said angiogenic proteins or peptides is selected from the group consisting of a fibroblast growth factor, a vascular endothelial growth factor, a platelet-derived growth factor, a hypoxia-inducible factor, an insulin-like growth factor and an angiogenic polypeptide regulator and wherein the second of said angiogenic proteins or peptides is selected from another member of said group.

146. The composition of claim 142, wherein the first of said angiogenic proteins or peptides is a fibroblast growth factor and the second of said angiogenic proteins or peptides is a vascular endothelial growth factor.

147. The composition of claim 142, wherein the first of said angiogenic proteins or peptides is a fibroblast growth factor or a vascular endothelial growth factor and the second of said angiogenic proteins or peptides is an insulin-like growth factor.

148. The composition of claim 142, wherein said vector comprises a transgene or transgenes encoding a fibroblast growth factor, a vascular endothelial growth factor and an insulin-like growth factor.

149. The composition of claim 121, wherein said vector further comprises a transgene encoding a cardiac enhancing protein or peptide.

150. The composition of claim 149, wherein said cardiac enhancing protein or peptide is a beta-adrenergic signaling protein or peptide (beta-ASP).

151. The composition of claim 121, further comprising a pharmaceutical excipient.

152. A kit comprising a gene therapy composition according to one of claims 121 to 151.

153. A kit of claim 152, further comprising a device for introducing the composition into a blood vessel or tissue in vivo.

154. A kit of claim 153, wherein the device is a catheter.

155. A kit of claim 152, further comprising a vasoactive agent.

156. A kit of claim 155, wherein the vasoactive agent is histamine.